EXPERT OPINION

Triple reuptake inhibitors: a patent review (2006 – 2012)

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Introduction: The dysfunctions of three very important monoamine neurotransmitters, serotonin (5-HT), norepinephrine (NE) and dopamine (DA), are associated with some of important CNS diseases such as depression; developing the triple reuptake inhibitors (TRIs) that can rebalance 5-HT, NE and DA through the inhibition of the monoamine reuptake transporters will lead to a more effective and safer antidepressant.
Areas covered: This article reviews past 7 years' advances in the development of TRIs; a patent review (2006 – 2012), covering the discovery of new chemical entities, and development status of leading TRI clinical candidates.
Expert opinion: The development of TRIs has several challenges, including discovering a "single" agent that has the activities against all three monoamine reuptake transporters SERT, NET and DAT. More important is that the agent must have a "right ratio" to be safer and better tolerated for the treatment of depression. The TRIs can potentially be used for the treatment of other CNS diseases, such as pain, Parkinson's and attention deficit hyperactivity disorder (ADHD), depending on ratios of SERT, NET and DAT.

Keywords: attention deficit hyperactivity disorder, depression, dopamine, monoamine transporters, neuropathic pain, neurotransmitter, norepinephrine, serotonin, structure–activity relationships, triple reuptake inhibitors

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1. Introduction

Serotonin, norepinephrine and dopamine are three very important monoamine neurotransmitters in the human brain [1]. Serotonin regulates mood, sleep, emotional states and some cognitive functions; norepinephrine regulates alertness and arousal, and influences on the reward system; dopamine plays a major role in reward-motivated behavior, mood regulatory functions, working memory, attention and executive functions [2]. The dysfunctions of these monoamine systems alone or in combination are associated with some important CNS diseases, such as depression, generalized anxiety disorder (GAD) and, social phobia, Parkinson's disease, attention deficit hyperactivity disorder (ADHD) and restless legs syndrome (RLS), etc.

Monoamine transporters (MATs) are a class of membrane transporter proteins that play important roles to regulate the concentration of extracellular monoamine neurotransmitters [3,4]. Serotonin transporter (SERT), norepinephrine transporter (NET) and dopamine transporter (DAT) are three major classes of MATs. Drugs classified as reuptake inhibitors have been one of the cornerstones of antidepressant treatment since the 1960s. The most widely known antidepressants are MATs inhibitors, such as selective serotonin reuptake inhibitors (SSRIs) [5] and serotonin–norepinephrine reuptake inhibitors (SNRIs).

As the first generation of MATs inhibitors, SSRIs were also the first class of antidepressants discovered using rational drug design approach [6]. As a class, SSRIs are generally better, more tolerated, safer than monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants (TCAs).

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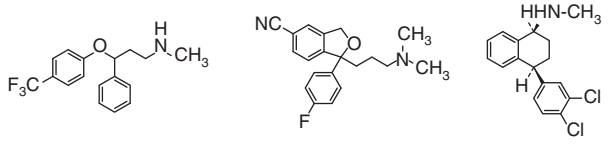
Article highlights.

- Serotonin (5-HT), norepinephrine (NE) and dopamine (DA) are associated with some of important CNS diseases such as depression.
- Developing the triple reuptake inhibitors (TRIs) that can rebalance 5-HT, NE and DA through the inhibition of the monoamine reuptake transporters will lead to a more effective and safer antidepressant.
- TRIs have also been implicated in the pathogenesis and treatment of neuropathic pain and ADHD.
- The progress for TRIs in general was slow and the biggest challenge is how to find an agent with a "right ratio" in practice.

This box summarizes key points contained in the article.



1 Fluoxetine **2** Citalopram **3** Sertraline

Figure 1. The first generation of MAT inhibitors.

Fluoxetine (trade names Prozac, Sarafem, Fontex, **1**) was developed by Eli Lilly [7] and was the first SSRI approved by US Food and Drug Administration (FDA) in 1987. The approved indications are major depressive disorder or MDD (adult and pediatric populations), obsessive-compulsive disorder (OCD, adult and pediatric populations), bulimia nervosa, panic disorder (PD) and premenstrual dysphoric disorder. Fluoxetine went off-patent in August 2001.

Citalopram (trade names Celexa, Cipramil, **2**) was originally discovered by Lundback in 1989, and was approved by US FDA in 1998 for MDD. The patent expired in 2003. In most European countries, it is approved for depressive episodes and PD with or without agoraphobia. In Spain, it is also used for OCD.

Sertraline hydrochloride (trade names Zoloft, Lustral, **3**) was introduced in the market by Pfizer in 1991 and became generic in 2006. Sertraline is approved for the treatments of MDD in adult outpatients as well as OCD, PD and social anxiety disorder (SAD) in both adults and children. Despite the availability of newer drugs, SSRIs remain extremely popular. In 2011, citalopram, sertraline and fluoxetine remained the top three most prescribed antidepressants on the US market (**Figure 1**).

As second generation of MATs inhibitors, dual uptake inhibitors such as venlafaxine **4**, milnacipran **5** and duloxetine **6** (**Figure 2**) offered better antidepressant efficacy [8]. Since the SNRI also regulates norepinephrine level in CNS system, this class drugs were used for treatment of other CNS disorders such as neuropathic pain, fibromyalgia, etc.

Venlafaxine (Effexor), developed by Wyeth in 1994, is the first and most commonly used SNRI. Venlafaxine is indicated for the treatment of MDD, GAD, SAD, and PD with or without agoraphobia. A dose-dependent effect on NE transporter inhibition is likely to account for the greater efficacy of venlafaxine at higher doses and may contribute to the dose-dependent increase in blood pressure [8].

Milnacipran (**Ixel**) is currently marketed for MDD in over 45 countries worldwide but not in US. it was first approved for the treatment of MDDs in France in December 1996. In January 2009, the US FDA approved milnacipran (brand name Savella) only for the treatment of fibromyalgia.

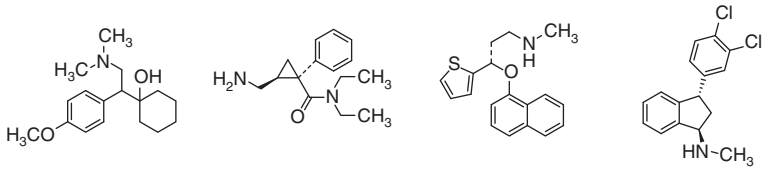
Duloxetine (Cymbalta) developed by Eli Lilly and Co., was for clinical use in the US for the treatment of depression and neuropathic pain. It was also approved for MDD, GAD, chronic musculoskeletal pain and fibromyalgia.

Both SNRIs and SSRIs share many of the same side effects in varying degrees. The most common include loss of appetite, weight and sleep. The slow onset is considered a big downside to treatment with SSRIs and SNRIs (slow onset of action of reuptake inhibitors has been a limitation). This therapeutic lag [9] is considered the result of slowly improving information processing in neural circuits via increased neurogenesis or increased plasticity of brain networks, stimulated over time by increased monoamine levels from current therapies [10]. The sexual dysfunction is also another significant problem for long-term treatment using these classes of drugs. Anhedonia, a core symptom of major depression, is also responding poorly, particularly, to SSRIs [11,12].

One strategy to reduce the therapeutic lag and/or to improve efficacy is the addition of a dopamine component to a dual reuptake inhibitor to create a triple reuptake inhibitor (TRI). Although the addition of dopamine reuptake inhibitors to existing therapies is not a new concept [13], there is mounting evidence that intervention resulting in decreasing catecholamine metabolites does produce a worsening of depressive symptoms in patients being treated with SSRIs and NRIs [14]. Bupropion, a dopamine and norepinephrine reuptake inhibitor, demonstrated antidepressant activities in clinical treatment [15]. It was also was used as augmentation with SSRI\SNRI for reducing sexual dysfunction.

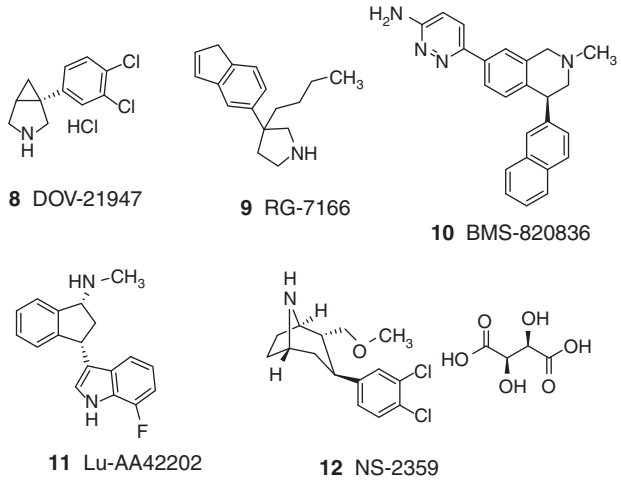
The concept of broad-spectrum antidepressants [16-19] was developed based on the fact that major depression is a heterogeneous and complex disorder attributed to many factors (include genetics, development and environment) [20,21] and growing evidence indicates that antidepressants with poly mechanism of action are more effective [22-24]. As a new generation of antidepressants, TRIs is aiming at an enhanced antidepressant response, the reduction of therapeutic lag or increased compliance due to a reduction of anhedonia and sexual dysfunction associated with typical SSRI use.

The history of discovery of chemical space for TRIs started decades ago. Indatraline (Lu 19-005) (7)discovered by Lundbeck is one of the first (if not the first) very potent TRIs with IC_{50} values 0.48, 0.26 and 0.99 nM for SERT, NET and



4 Venlafaxine **5** Milnacipran **6** Duloxetine **7** Lu 19005

Figure 2. The second generation of MAT inhibitors.



8 DOV-21947 **9** RG-7166 **10** BMS-820836

11 Lu-AA42202 **12** NS-2359

Figure 3. Examples of MAT inhibitors under development.

DAT, respectively (inhibition of ^{3}H-amine uptake into rat brain synaptosomes) [25,26].

During 2006 through 2012, there are 146 patent publications related to TRI. Based on the Thomson Pharma survey, the following compounds are listed in the development database.

Amitifadine hydrochloride (EB-1010, DOV-21947, **8**) is being developed by Euthymics Bioscience, following its acquisition of DOV Pharmaceuticals. A capsule formulation of the TRI, structurally related to DOV-216303, has been studied for the potential treatment of depression and obesity. A Phase IIb/IIIa, multicenter, double-blind, placebo-controlled, 12-week, safety and efficacy trial (TRIADE) was initiated in March 2011, and the top-line results were reported in May 2013 that amitifadine did not show a significant difference from placebo in the primary endpoint of change in the Montgomery–Asberg depression rating scale (**Figure 3**).

Euthymics Bioscience is also developing EB-1020, a non-stimulant TRI for the potential treatment of adult ADHD and is investigating its potential use in the treatment of neuropathic pain. In March 2012, a Phase I study for adult ADHD was initiated in healthy subjects.

SEP-225289 was developed by Sepracor (now Sunovion), a subsidiary of Dainippon Sumitomo Pharma America, for the potential treatment of MDD and possible other CNS conditions such as substance abuse. In July 2009, Sepracor reported that the drug had failed the primary endpoint in a Phase-II clinic trial. In 2010, Dainippon stated that based on the results of a portfolio priority evaluation, SEP-225289 was discontinued.

The structure of SEP-225289 was not published. It blocked human recombinant SERT, NET and DAT with IC_{50} values of 15, 4 and 3 nM, respectively. In a mouse *ex vivo* occupancy study, the SEP-225289 showed IC_{50} values 10, 5 and 1 mg/kg po., respectively.

SEP-228425 and SEP-228432 (structures not disclosed) were also in their Phase I clinic trials for potential indications of pain, MDD and ADHD. No detail was reported.

RG-7166 (**9**) was developed by Roche Holding AG. Phase I development began in the 4Q of 2009. In February 2012, the development of RG-7166 was discontinued, and the reason was not disclosed.

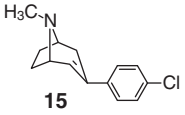
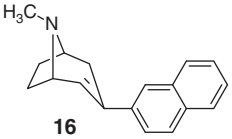
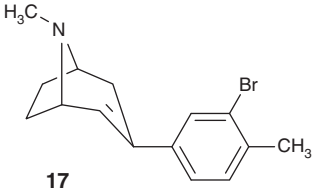
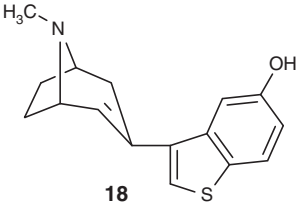
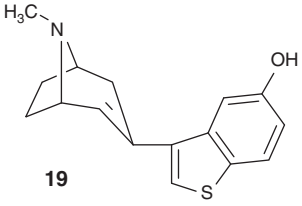
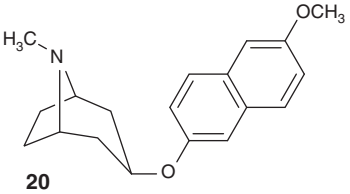
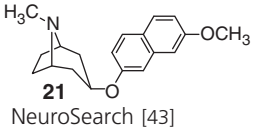
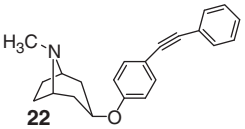
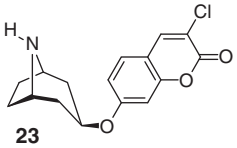
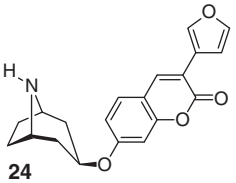
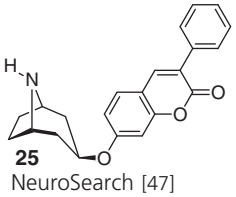
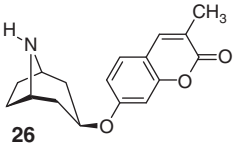
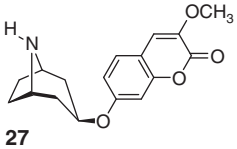
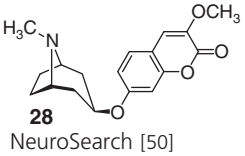
BMS-820836 (**10**) was developed by Bristol-Myers Squibb for the potential oral treatment of depression. This is one compound from a series of TRIs licensed from AMRI (Albany Molecular Research). A randomized, double-blind, multiple-dose, Phase I trial with safety and tolerability as the primary outcome and the pharmacodynamics as secondary outcome, was completed in November 2010. Two Phase IIb trials failed and further studies of the drug were cancelled.

BMS-866949, a second candidate from the BMS/AMRI series of TRIs, was selected for preclinical development in September 2008. A Phase I, single ascending dose trial was completed in March 2010; a Phase I, multiple ascending dose trial was initiated in May 2010. A Phase I, multiple ascending dose trial had been terminated early in March 2012 and reason was unknown.

Lu-AA42202 (**11**) is being investigated by Lundbeck for the potential treatment of MDD and ADHD. IC_{50} values of Lu-AA42202 for SERT, DAT and NET were 8.1, 14 and 9.3 nM, respectively.

NS-2359 (GSK-372475; 372475, **12**) was developed by GlaxoSmithKline (GSK), under license from NeuroSearch for the potential treatment of depression. In February 2009, two Phase II trials failed to meet the primary endpoint that led to discontinuation of the development for depression. NeuroSearch also suspended Phase II for ADHD.

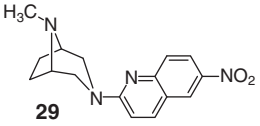
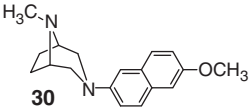
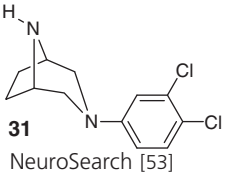
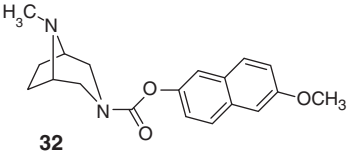
Table 1. Neurotransmitter uptake inhibition of cocaine derived tropane analogs.

Structure	Uptake inhibition*‡ IC_{50} (nM)			Structure	Uptake Inhibition*‡ IC_{50} (nM)		
	SERT	NET	DAT		SERT	NET	DAT
 **15** NeuroSearch [36]	4.7	26	79	 **16** (–)–enatiomer NeuroSearch [37]	0.23	18	34
 **17** NeuroSearch [38]	1.4	15	13	 **18** NeuroSearch [39]	0.37	4.3	94
 **19** NeuroSearch [42]	2.5	27	220	 **20** NeuroSearch [43]	26	15	420
 **21** NeuroSearch [43]	0.42	500	1400	 **22** NeuroSearch [44]	720	79	24
 **23** NeuroSearch [45]	0.59	14	54	 **24** NeuroSearch [46]	10	0.48	9.9
 **25** NeuroSearch [47]	6.0	19	48	 **26** NeuroSearch [48]	0.76	11	170
 **27** NeuroSearch [49]	2.9	3.8	70	 **28** NeuroSearch [50]	4.4	9.2	9.5

*The neurotransmitter uptake inhibitory effects of compounds were conducted in preparations of synaptosomes from different brain regions of male Wistar rats (NE: hippocampi; DA: corpi striate; SERT: cerebral cortices).

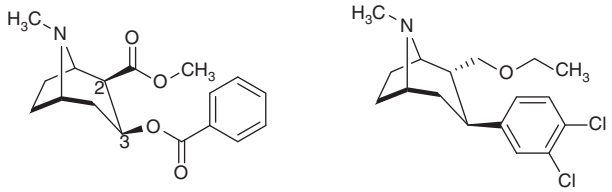
‡The test values are given as IC_{50} (the concentration (nM) of the test substance that inhibits the specific binding of ^{3}H-DA, ^{3}H-NE or ^{3}H-SERT by 50%).

Table 1. Neurotransmitter uptake inhibition of cocaine derived tropane analogs (continued).

Structure	Uptake inhibition*‡ IC_{50} (nM)			Structure	Uptake Inhibition*‡ IC_{50} (nM)		
	SERT	NET	DAT		SERT	NET	DAT
 **29** NeuroSearch [52]	3.1	4600	16000	 **30** NeuroSearch [54]	20	20	56
 **31** NeuroSearch [53]	0.69	7.4	160	 **32** NeuroSearch [54]	340	24	30

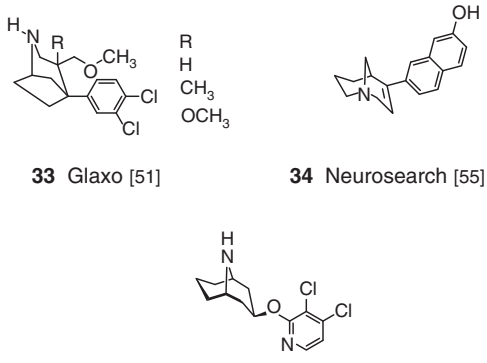
*The neurotransmitter uptake inhibitory effects of compounds were conducted in preparations of synaptosomes from different brain regions of male Wistar rats (NE: hippocampi; DA: corpi striate; SERT: cerebral cortices).

‡The test values are given as IC_{50} (the concentration (nM) of the test substance that inhibits the specific binding of ^{3}H-DA, ^{3}H-NE or ^{3}H-SERT by 50%).



13 Cocaine **14** Tesofensine (NS2330)

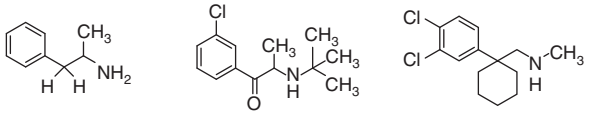
Figure 4. The prototypes of tropane analogs.



33 Glaxo [51] **34** Neurosearch [55]

35 N.V. Organon [56]

Figure 5. Examples of 2-azabicyclo [3,2,1]octanes reported by Glaxo, NeuroSearch and N.V. Organon.



36 Amphetamine **37** Bupropion **38** Shao L, [58]

Figure 6. Amphetamine and its structural analogs.

NeuroSearch was also developing the NSD-788 for the potential treatment of psychiatric disorders, including anxiety and depression. In August 2009, NeuroSearch completed a Phase I study and a clinical proof-of-mechanism trial, no structure and detail pharmacological profile information were reported.

2. Patent review (2006 – 2012, 7 years)

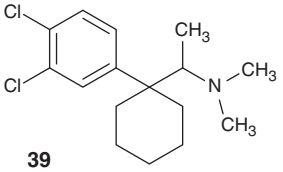
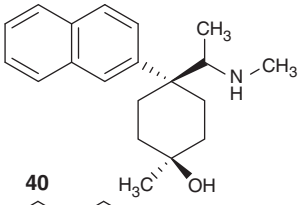
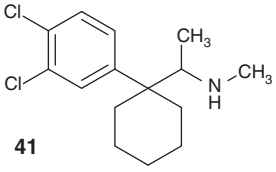
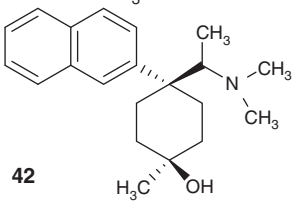
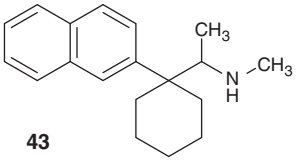
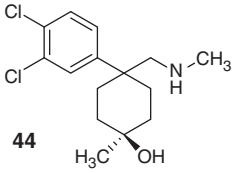
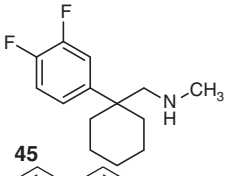
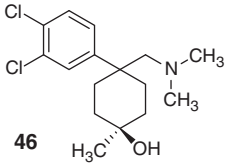
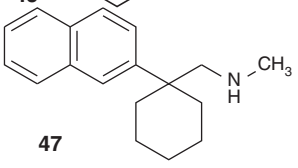
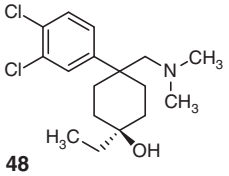
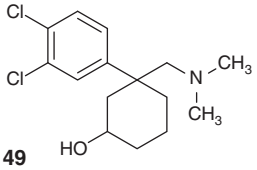
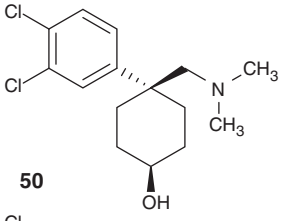
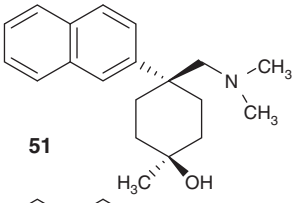
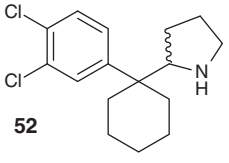
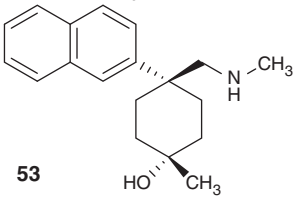
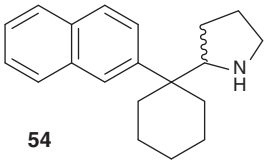
2.1 Cocaine-derived tropane analogs (Table 1)

2.1.1 Cocaine and tesofensine

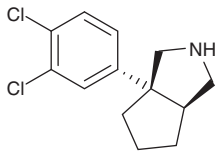
Tropanes remain one of the most investigated monoamine reuptake inhibitors. Cocaine (**13**) is a naturally occurring tropane alkaloid, which has been used and abused as a stimulant, appetite suppressant or topical anesthetic for a long history. Biologically, it is a serotonin–norepinephrine–dopamine reuptake inhibitor (SNDRI). Due to its diverse pharmacological activities and chemical instability, numerous structure modifications were made to improve its chemical stability, to minimize local anesthetic activity and to balance the inhibition profiles among various monoamine reuptake transporters. In most cases, the conservative tropane scaffold of cocaine remains unchanged (**Figure 4**).

Early investigations on 2-(ethoxymethyl)-tropanes removed the common structural motif for local anaesthetics and chemically unstable ester groups and yielded Tesofensine (NS2330) (**14**) [27,28]. The patent of hydrochloride salt form of this compound was filed by Glaxo Group [29], and its solid pharmaceutical preparation was patented by Boehringer [30]. Tesofensine was described to be a valuable pharmaceutical candidate for the treatment of various disorder of the central nervous system, including stimulation of cerebral progenitor proliferation and improvement of synaptic plasticity [31]. It is a useful candidate for the treatment of patients with mental diseases in the advanced stages [32]. Moreover, it has also been claimed to be a potential treatment for sexual desire disorders [33] and overeating disorders [34], as well as addiction therapies [35].

Table 2. Neurotransmitter uptake inhibition* of cycloalkylamines (Sepracor [57]).

Structure	Uptake inhibition IC_{50} (nM)			Structure	Uptake inhibition IC_{50} (nM)		
	SERT	NET	DAT		SERT	NET	DAT
 **39**	12	10	36	 **40**	63	19	83
 **41**	81	57	30	 **42**	18	33	21
 **43**	6	23	63	 **44**	210	55	71
 **45**	51	67	57	 **46**	34	13	41
 **47**	34	295	90	 **48**	20	41	37
 **49** (cis-isomer)	44	17	3	 **50**	84	18	22
 **51**	7	23	167	 **52**	73	87	27
 **53**	11	33	40	 **54**	40	57	13

*The recombinant human serotonin transporter expressed in HEK-293 cells, the recombinant human dopamine transporter expressed in either CHO-K1 or HEK293 cells and the recombinant human norepinephrine expressed in either HEK293 or MDCK cells were used in the assays of neurotransmitter uptake inhibition.



55 Sepracor [60]

Figure 7. Selected bicyclic compound from the patent WO2010075064.

2.1.2 *8-azabicyclo[3,2,1]octenes (Table 1)*

Besides 2-alkoxy-3-aryl-tropanes (e.g., cocaine and tesofensine), 8-azabicyclo[3.2.1]oct-2-ene derivatives were also investigated and claimed. Based on their previous work on racemic 3-(4-chlorophenyl)-8H- 8-aza-bicyclo[3,2,1]oct-2-ene analogs (**15**) [36], NeuroSearch described novel monoamine neurotransmitter reuptake inhibitors. Among these compounds, (-)-8-methyl-3-(naphthalen-2-yl) -8-azabicyclo [3.2.1]oct-3-ene is a selective SERT inhibitor (**16**) [37], while (±)-3-(3-Bromo-4-methylphenyl)-8-azabicyclo [3.2.1]oct-3-ene is a low-nanomolar inhibitor against various reuptake transporters (**17**) [38].

Recently, analogs with benzo[b]thiophen-2-yl substitution were also patented as 8-azabicyclo[3.2.1]oct-2-ene bioisosteres that have similar reuptake inhibitory activities (**18**) [39].

In 2009, Boehringer Ingelheim claimed a synthetic approach to prepare structurally novel 8-azabicyclo[3,2,1] octenes, which provides accessibility to novel 8-azabicyclo [3,2,1]octenes with more structural diversity [40].

2.1.3 *8-azabicyclo[3,2,1]octane ethers (Table 1)*

In 2006, NeuroSearch claimed a preparation method for novel 8-alkyl-3-perfluoroalkylsulfonyloxy -8-azabicyclo[3.2.1]oct-3-ene [41]. This key intermediate led to the preparation of novel 8-azabicyclo[3,2,1]octane ethers that share similarities with typical 8-azabicyclo[3,2,1]octenes (**19**) in reuptake inhibitory activities [42]. Moreover, some structurally saturated 8-azabicyclo[3,2,1]octane ethers (**20 – 21**) have been found to be dual acting SERT/DA reuptake inhibitors or highly SSRIs [43]. Among these compounds, a phenylethynyl derivative (**22**) was disclosed to be a norepinephrine/dopamine dual reuptake inhibitor [44]. Quinuclidine and phenoxazin-3-one derivatives were claimed as bioisosteres of 8-azabicyclo [3,2,1]octane ethers with reasonable selectivity and activity upon monoamine reuptake transporters. Besides, chromen-2-one derivatives are among the most investigated bioisosteres. Early disclosed exo-7-(8-aza-bicyclo[3.2.1]oct-3-yloxy) -3-chloro-chromen-2-one (**23**) has an IC_{50} of 54 nM against DA, 14 nM against NA and 0.59 nM against SERT reuptake [45], while exo-7-[(1*S*,3*S*,5*R*)-(8- azabicyclo[3.2.1]octan-3-yl)oxy]-3-(furan-3-yl)-chromen-2-one (**24**) is a novel TRI with an IC_{50} of 48 nM against DA, 19 nM against NA and 6.0 nM against SERT reuptake [46]. The potential use of other chromen-2-one derivatives with variable monoamine reuptake inhibitory activities was also claimed, including the most potent triple inhibitor exo-3-methoxy-7-[(8-methyl-8-azabicyclo[3.2.1] octan-3-yl)oxy]-chromen-2-one (**25 – 28**) in this structure categories [47-50].

2.1.4 *2-Azabicyclo[3,2,1]octanes*

Besides of their work on Tesofensine, Glaxo claimed novel 2-azabicyclo [3,2,1]octanes with some affinities to all three monoamine uptake transporters. These compounds are structural alternations of 8-azabicyclo[3,2,1]octanes (**33**) (**Figure 5**) [51].

2.1.5 *Diazabicyclic analogs (Table 1)*

Diazabicyclic analogs are bioisosteres of tropanes. NeuroSearch described a 3, 9-diazabicyclo[3,3,1]nonane derivative with a 3-(6-nitroquinolin-2-yl) substitution (**29**) to be a highly SSRI, while another derivative with 3-(6-methoxynaphthalen-2-yl) substitution (**31**) shows more balanced TRI activities [52,53].

In other diazabicyclic analogs such as 8-diazabicyclo[3.2.1] octane- (**30**)and 3,9- diazabicyclo[3.3.1]nonane-3-carbamates, 9-methyl-3,9-diazabicyclo [3.3.1] nonane-3-carboxylic acid 6-methoxynaphthalen-2-yl ester (**32**) was also claimed to have favorable dual NA/SERT inhibition activities [54].

2.1.6 *Ring-expanded tropanes*

1-Aza-bicyclo[3.3.1]non-3-enes [55] (**34**) and 9-azabicyclo [3,3,1]nonane aryl ethers [56] (**35**) are both ring-expanded tropanes with TRI activities. But some of these compounds were described to have opioid-like effects [57].

2.2 Amphetamine-derived analogs

2.2.1 *Cycloalkylamines*

Cycloalkylamines are structural analogs of the well-studied amphetamine (**36**) and bupropion (**37**), with an additional cycloalkyl group substitution. The prototype compound of cycloalkylamines was identified from rational design approaches. The hit compound [58] (**38**)was reported to have a desirable profile at all three uptake transporters and a long half-life in human liver microsomes *in vitro*. Sepracor, Inc., expanded the scope of this structural class by utilizing substitution, asymmetric and ring-fusion strategies (**Figure 6**) [59].

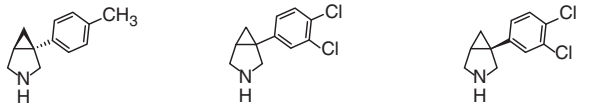
The described cycloalkylamines are low-nanomolar inhibitors against all three monoamine reuptake transporters and they have acceptable metabolic stability *in vitro*, as well as brain-penetrating capabilities. The reuptake inhibition activities *in vitro* for exemplified selective compounds were shown in **Table 2**.

It should be noted that some compounds had also been evaluated in the models of mouse tail suspension test and rat forced swim test *in vivo*, which was considered to be predictive of antidepressant activity in humans. Rat locomotor activity was also used to check the specificity of antidepressant effects. In the mouse tail suspension and locomotor activity test (rat or mice), all tested compounds exhibited an

Table 3. The binding affinities of 1-(3, 4-dichlorophenyl)-3-azabicyclo[3,1,0] hexane and its enantiomers at the biogenic amine transporters Dov [65].

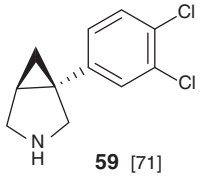
Compound		Binding affinities K_i (nM)		
		SERT*	NET‡	DAT§
DOV 216,303	(±)-1-(3,4-chlorophenyl)-3-azabicyclo [3,1,0]hexane	187	142	154
DOV216,947	(+)-1-(3,4-chlorophenyl)-3-azabicyclo [3,1,0]hexane	99¶	262¶	213¶
DOV102,677	(-)-1-(3,4-chlorophenyl)-3-azabicyclo [3,1,0]hexane	N/A	N/A	261
GBR 12909				11.6
Desimipramine			1.13	
Imipramine		26.4		

*The receptor source was rat forebrain membranes; the radio ligand was [^{3}H]citalopram (70 – 87 Ci/mmol) at a final ligand concentration of 1.0 nM.
‡The receptor source was rat forebrain membranes; the radio ligand was [^{3}H]nisoxetine (60 – 85 Ci/mmol) at a final ligand concentration of 1.0 nM.
§The receptor source was guinea pig striatal membranes; the radio ligand was [^{3}H] WIN 35,428 (60 – 87 Ci/mmol) at a final ligand concentration of 2.0 nM.
¶Data from HEK293E cell lines assays expressing human NE, DA and SERT transporters.
N/A: No measurable affinity.



56 Bicifadine **57** DOV 216, 303 **58** DOV102, 677

Figure 8. Bicifadine and its analogs disclosed by DOV.



59 [71]

Figure 9. Selected enatiomer of DOV 216, 303 from the patent WO2007016155 disclosed by DOV.

antidepressant-like profile (i.e., significantly decreased immobility time) in the range of 3 – 30 mg/kg, PO. In the tail suspension test, no change or a decrease in baseline motor activity was observed indicating that antidepressant-like activity was not due to a general stimulant effect. In the rat forced swim and locomotor activity tests, all tested compounds exhibited antidepressant-like effects in the range of 10 – 30 mg/kg, PO. Moreover, the decrease in immobility produced by these compounds appeared to be due to increase in swimming and climbing behaviors indicative of mixed transporter activity (i.e., SNRI profiles).

2.2.2 Bicyclic compounds

Bicyclic compounds are ring-constrained cycloalkylamines with TRI activities (55) [60]. Besides antidepression evaluation *in vivo*, the analgesia effect of a bicyclic compound, (3aR, 6aS)-3a-(3, 4-dichlorophenyl) octahydrocyclopenta [c]pyrrole, was also evaluated for acute and persistent inflammatory pains in male rats. The administration of this compound resulted in a significant, dose-related decrease in formalin induced flinching behavior of Phase I (the result of C-fiber activation) and selective attention of Phase II (the combination of an inflammatory response in the tissue and functional changes in the dorsal horn of the spinal cord). By contrast, the administration of gabapentin marketed as a neuropathic analgesic resulted in a significant and selective attenuation of Phase II formalin-induced flinching behavior only (**Figure** 7).

2.3 3-Azabicyclo[3,1,0]hexanes and analogs

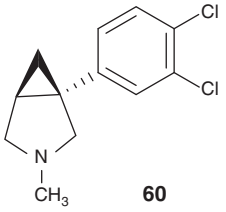
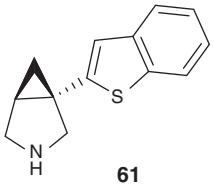
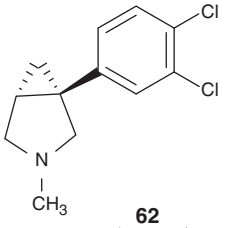
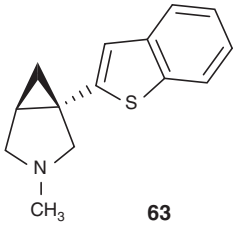
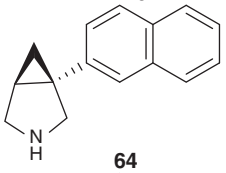
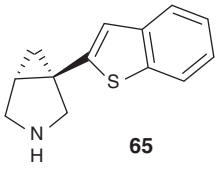
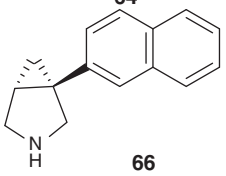
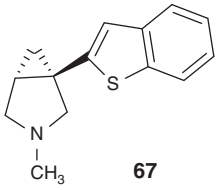
2.3.1 3-Azabicyclo[3.1.0]hexanes

Azabicyclo[3,1,0]hexanes with mono-aromatic substitution, exemplified by bicifadine (DOV-220,075, 56) and 1-(3, 4-dichlorophenyl)-3-azabicyclo [3,1,0] hexane (DOV-216,303, 57), were developed by DOV Pharmaceutical and found to inhibit the uptake of biogenic amines in the central nervous system [61-64].

DOV-216,303 has been recognized to be an SNDRI due to its multiple monoamine reuptake inhibitory activities. This compound has been implicated in a wide variety of neuropsychiatric disorders ranging from anxiety and depression to eating disorders and drug addiction. The TRI activities of this compound suggest a possible use of the compound as a "broad spectrum antidepressant" with advantages of more rapid onset and/or higher efficacy of antidepressant activity in comparison to currently available antidepressants, including agents that inhibit mono- or dual reuptake of serotonin and/or norepinephrine [16,18].

Due to the presence of two chiral carbons, there should be four potential stereoisomers for DOV 216, 303 theoretically. Among these isomers, (-)-1-(3, 4-dichlorophenyl)-3-azabicyclo

Table 4. Neurotransmitter uptake inhibition of 1-aryl-3-azabicyclo[3,1,0] hexanes [71,72].

Structure	Uptake Inhibition* IC_{50} (nM)			Structure	Uptake Inhibition‡ IC_{50} (nM)		
	SERT	NET	DAT		SERT	NET	DAT
 **60**	23	19	120	 **61**	193	14	52
 **62**	87	82	130	 **63**	54	71	224
 **64**	65	< 10	49	 **65**	481	99	149
 **66**	170	56	98	 **67**	263	104	195

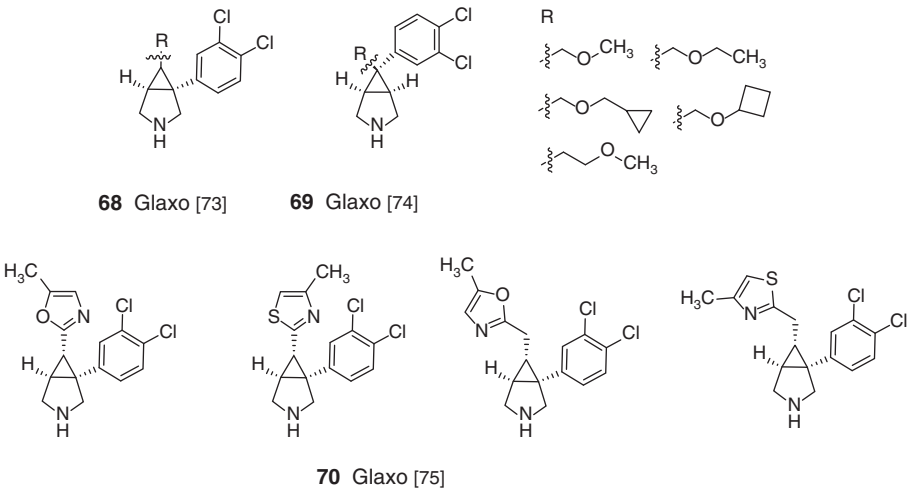
*The neurotransmitter uptake inhibitory effects of compounds were conducted in preparations of synaptosomes from different rat brain regions (NE: rat hypothalamus; DA: rat striatum synaptosomes; SERT: rat brain synatosomes).

‡The neurotransmitter uptake inhibitory effects of compounds were conducted in cell lines recombinantly expressing human transporters (HEK 293 cells expressing SERT transporter; MDCK cells expressing the NE transporter, and CHO-K1 cells expressing the DA transporter).

3, 1, 0]hexane (DOV 102,677, **58**) was described to be separated from its (+)-antipode. Surprisingly, the binding assays showed that DOV 102,677 blocked dopamine transport only, but not norepinephrine or serotonin uptake (the binding affinities of these enatiomers are shown in **Table 3**). Although this compound remained some affinities for recombinant norepinephrine or serotonin uptake transporters, these activities were significantly less than those of its enatiomer DOV 216,947 (**8**), as well as its racemic mixture DOV21, 303.

In high ethanol-preferring (HEP) rat assays *in vivo*, the administration of DOV 102,677 had pronounced effects on the volitional consumption of ethanol associated with little change in food consumption in the mHEP rat, which was not due to an adipsic action of the compound. Therefore, DOV 102, 677 was claimed to treat or prevent a disorder alleviated by inhibiting dopamine uptake without the side effects relevant to cardiovascular effects, sleep interruption, hypertension or sex dysfunction associated with norepinephrine or serotonin uptake inhibitors [65].

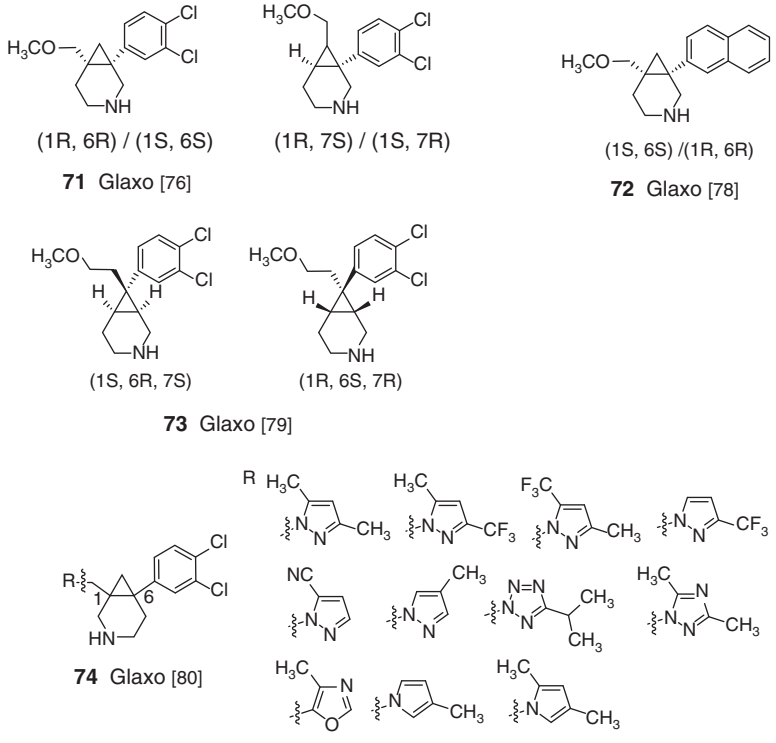
Moreover, the (+) optical antipode (DOV 21, 947) (**Figures 3**, **8**) of 1-(3, 4-dichlorophenyl)-3-azabicyclo[3,1,0] hexane was claimed to have a significantly greater affinity for norepinephrine uptake transporter and serotonin uptake site than does the racemic mixture, and thus this compound might be more active. Novel polymorph of DOV 21, 947 was also described [66]. In the diet-induced models of obesity (DIO), the administration of this compound could reduce the body weight as a result of selective decrease in fat mass. Moreover, under the dosage of 20 mg/kg/D, DOV 21,947 could selectively reduce retroperitoneal and mesenteric mass, but not epididymal fat deposits. The body mass loss persisted during DOV 21947 treatments, but it was reversible upon cessation of treatment. After 14 days of administration, DOV 21,947 (6 mg/kg BID, 20 mg/kg/day) significantly decreased plasma triglyceride. Meanwhile, the no-observed-adverse levels (NOAELs) for oral administration of DOV 21,947 to rats and dogs for 13 weeks were determined to be 10 and 6.0 mg/kg/day, respectively, in



68 Glaxo [73] **69** Glaxo [74]

70 Glaxo [75]

Figure 10. Selected examples of 3-azabicyclo[3.1.0] hexanes disclosed by GLAXO.



(1R, 6R) / (1S, 6S)

71 Glaxo [76]

(1R, 7S) / (1S, 7R)

(1S, 6S) /(1R, 6R)

72 Glaxo [78]

(1S, 6R, 7S) (1R, 6S, 7R)

73 Glaxo [79]

74 Glaxo [80]

Figure 11. Selected examples of 3-azabicyclo[4.1.0]heptanes disclosed by GLAXO.

toxicokinetic studies. In addition, the results from the DIO rats are predictive of the human condition, in that overweight subjects treated with DOV 21,947 manifested a significant decrease in body weight and plasma triglyceride levels in a multiple-dose, randomized, double-blind, placebo-controlled safety and tolerability study of DOV 21,947 conducted on healthy subjects with overweight to moderately obese. Therefore, the pharmacological profile of this compound was described to be similar to that of sibutramine and DOV 21,947 was claimed to have surprisingly effectively appetite-reducing and/or weight-controlling activities [67].

Inspired by discovery of 1-(3, 4-dichlorophenyl)-3-azabicyclo[3,1,0]hexane, Corley et al. developed a relatively simple, short and highly efficient synthetic approach towards (1*R*, 5*S*)-(+)-1-(3,4-dichlorophenyl)-3 –azabicyclo[3,10]hexane with (R)-(-)- epichlorohydrin as the chiral source of starting

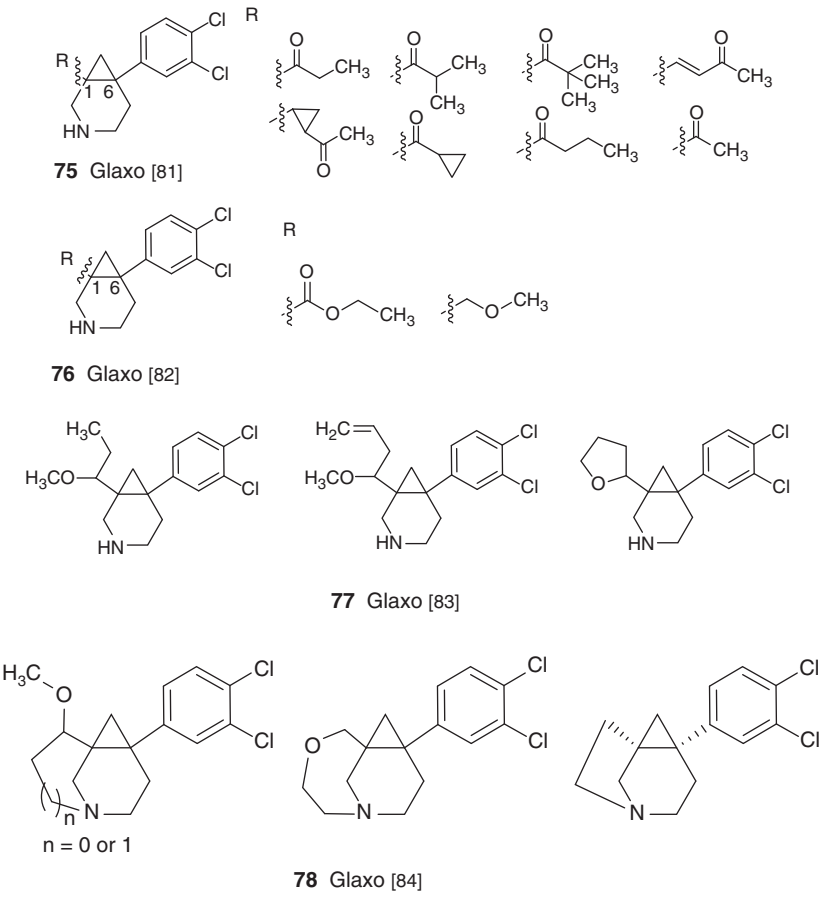


Figure 12. Selected examples of 3-azabicyclo[4.1.0]heptanes with special substituents disclosed by GLAXO.

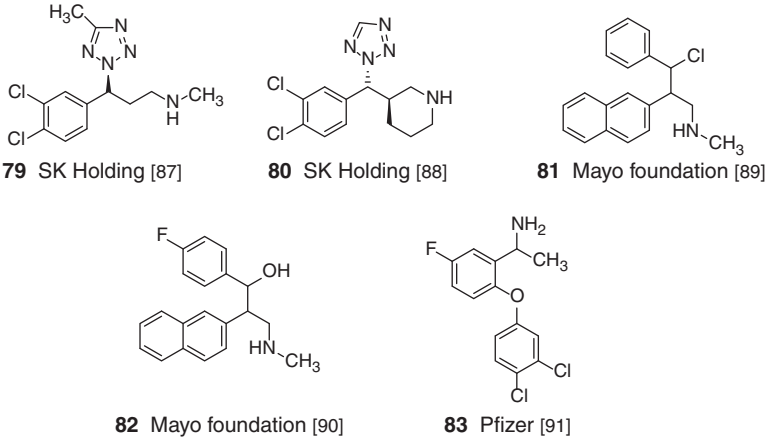


Figure 13. Selected examples of 3-phenylpropan-1-amines and analogs.

material [68]. Other enatiomeric pure 1-aryl-3-azabicyclo [3,1,0]hexanes were also claimed [69]. The efficacy and safety of (+)-1-(3, 4-dichlorophenyl)-3-azabicyclo[3,1,0]hexane hydrochloride (EB-1010) were further evaluated in patients with MDD [70]. This Phase II study demonstrated that EB-1010, at a titrated dose of 50 mg/day then 100 mg/day, was effective for treatment of patients with MDD. Efficacy was observed on the primary and secondary standard validated depression outcome measures (MADRS; global severity and improvement) as well as on the anhedonia factor of the

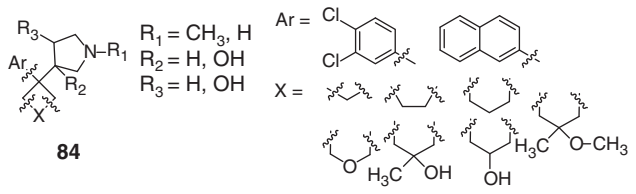


Figure 14. Selected pyrrolidine derivatives from the patent WO2010091268 disclosed by Sepracor.

MADRS. Overall, treatment with EB-1010 was well tolerated. Meanwhile, EB-1010 was not associated with weight gain or sexual dysfunction.

Skolnick et al. made further structural modifications based on the basic structural motif of DOV 216,303 (**59**) [71]. A series of multiple-substituted 1-aryl-3-azabicyclo[3,1,0]hexanes were prepared and preliminary biological assays yielded inhibitors with diverse activities whereby the absolute potency at any one transporter may be altered dramatically as shown in **Table 4** for the exemplified compounds. These evidences demonstrated powerful and unpredictable nature of these compounds, and might further evince the ability to fulfill additional therapeutic uses within the invention for treating diverse CNS disorders (**Figure 9**).

Other 1-heteroaryl -3-azabicyclo[3,1,0]hexanes with heteroaryl substitution were also claimed to have diverse TRI activities (**Table 4**) [72].

Besides of DOV's works, GLAXO are also committed to the development of 3-azabicyclo[3.1.0] hexanes. Early disclosed 3-azabicyclo[3.1.0]hexanes showed low affinities to three mono-amine reuptake transporters (**68**) [73]. However, by using aryl substitution migration strategy, novel 1-aryl-3-azabicyclo[3.1.0]hexane analogs were claimed to be much more active, with a pKi against SERT from 7.8 to 10.1; against NET from 7.1 to 9.9; and against DAT from 6.6 to 7.7 (**Figure 10**) (**69-70**) [74,75].

2.3.2 *3-Azabicyclo[4.1.0]heptanes*

3-Azabicyclo[4.1.0]heptanes are ring-expanded 3-azabicyclo [3.1.0]hexanes. Some 3-azabicyclo[4.1.0]heptanes have an alkyloxy substitution in the conservative cyclopropane (**71**) [76,77]. Other filed compounds include 6-[(methyloxy) methyl] -1-(2-naphthalenyl)-3-azabicyclo[4.1.0] heptanes and 7-aryl 3-azabicyclo[4.1.0] heptanes with 7-position substation (**72 – 73**) [78,79]. Compounds with 6-aryl substitution were also claimed to have a pKi against SERT from 7.2 to 10; against NET from 5.0 to 9.4; and against DAT from 6.2 to 9.8 (**Figure 11**) (**74**) [80].

Aliphatic ketone substituents were also introduced to the structure of 3-azabicyclo[4.1.0]heptanes to afford compounds with improved TRI activities (**75**) [81]. Other compounds with alkyloxycarbonyl and alkyloxyalkyl substituents were claimed (**76**) [82]. Moreover, compounds with alkyl substituents could afford an average pKi ≥ 8.5 against SERT; pKi ≥ 8.2 against NET; and pKi ≥ 8.0 against DAT (**Figure 12**) (**77**) [83].

Conformationally constrained compounds were designed and synthesized. The resulting afford tricycle azabicyclo [4.1.0]heptane derivatives with an average pKi ≥ 6.9 for hSERT; pKi ≥ 5.5 against hNET; and pKi ≥ 5.7 against hDAT (**78**) [84].

2.4 3-Phenylpropan-1-amine and its analogs

SSRIs are among the most prescribed antidepressants worldwide. Typical SSRIs contain a 3-phenylpropan-1-amine or similar scaffolds in their chemical structures. Considering their drug-likeness properties, well acknowldged safety profile and clinical experience, there remains much interest to develop monoamine reuptake inhibitors from the successfully marketed structures of fluoxetine (**1**), paroxetine, citalopram (**2**), fluvoxamine or other SSRIs.

Citalopram is one of the best-sold antidepressant with a diaryl group substitution in its chemical structure. N-methyl-citalopram was designed and synthesized to exert serotonin uptake activity in the peripheral system while being devoid of CNS activities [85].

Milnacipran (**5**), a cyclopropanecarboxamide analog of 3-phenylpropan-1-amine and a dual SERT/NA reuptake inhibitor, was claimed in the prevention or treatment of stress-related disorders [86], in addition to its approved application in the treatment of major depressive episodes and fibromyalgia.

2.4.1 *Multiple substituted 3-phenylpropan-1-amines and analogs*

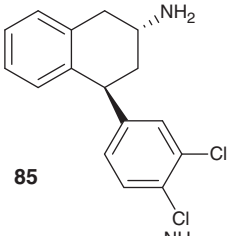
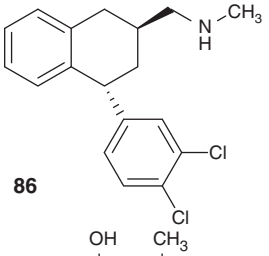
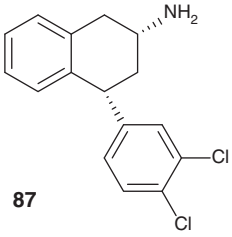
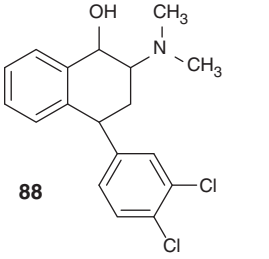
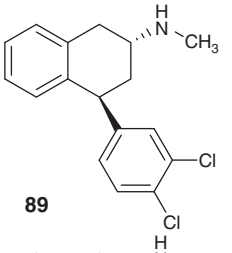
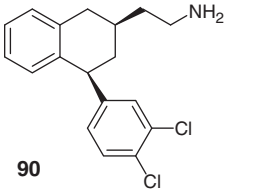
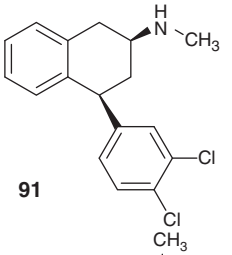
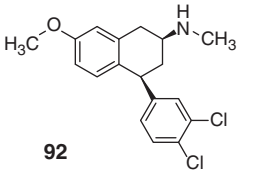
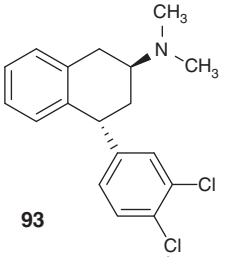
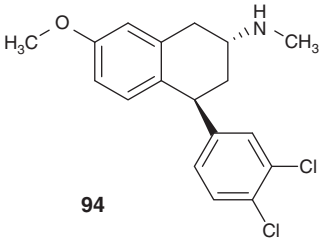
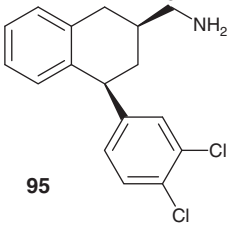
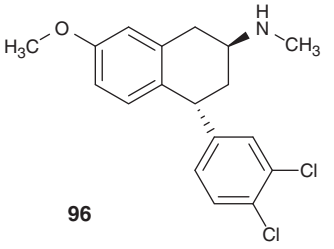
SK Holding claimed a series of 3-substituted propanamine derivatives as fluoxetine analogs, which have high inhibition potency of the serotonin, norpinephrine and dopamine transporter reuptake. *In vivo* studies showed that these compounds have therapeutic potential in the treatment of depression (forced swimming test), anxiety (marble burying test) and pain (acetic acid induced writhing test) (**79**) [87].

Ring-constrained analogs of 3-substituted propanamines were claimed to bear similar biological activities to those of 3-substituted propanamine derivatives in both *in vitro* and *in vivo* assays (**80**) (**Figure 13**) [88].

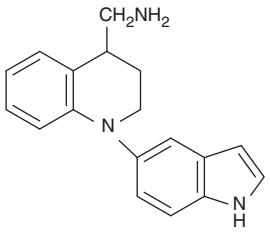
3-chloro-N-methyl-2-(naphthalen-2-yl)-3-phenylpropan-1-amine and related stereoisomers (**81**) [89] were described to be potential antidepressant activities *in vivo*, without increasing animal locomotor activities. Other similar compounds with neurotransmitter reuptake inhibition activities were claimed in 2011(**82**) [90].

Pifzer also got involved in the researches of similar analogs, and the claimed compound, 1-[2-(3, 4-dichlorophenoxy)-5-fluorophenyl]-ethylamine, was found to be a monoamine reuptake inhibitor. Meanwhile, diverse biological activities were noted for its enantiomers: racemic mixture (3.3, 5.3, 7.5 nM for SERT, DA and NA, respectively), (-)-R isomer

Table 5. Neurotransmitter uptake inhibition* of tetralone-based analogues.

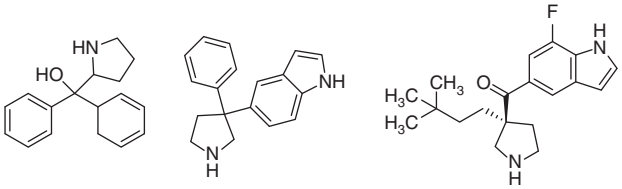
Structure	Uptake inhibition IC_{50} (nM)			Structure	Uptake inhibition IC_{50} (nM)		
	SERT	NET	DAT		SERT	NET	DAT
 **85**	46	124	350	 **86**	54	126	103
 **87**	108	174	175	 **88**	48	65	48
 **89**	6	27	114	One isomer  **90**	79	158	50
 **91**	8	45	281	 **92**	29	112	109
 **93**	108	174	176	 **94**	105	198	92
 **95**	2	28	11	 **96**	209	111	78

*The recombinant human serotonin transporter expressed in HEK-293 cells, the recombinant human dopamine transporter expressed in either CHO-K1 or HEK293 cells and the recombinant human norepinephrine expressed in either HEK293 or MDCK cells were used in the assays of neurotransmitter uptake inhibition.



97 Roche [96]

Figure 15. The structure of 1-(1*H*-indol-5-yl)-1, 2, 3, 4-tetrahydroquinolin-4-yl]-methyl-amine), an tetralone analog.



98 D2PM **99** Roche [97] **100** Roche [98]

Figure 16. Diphenylprolinol and its derivatives disclosed by Roche.

(225, 3.2, 3.2 nM) and (+)-S-isomer (2.3, 40.5, 22.9 nM) (**83**) [91].

Sepracor claimed a series of pyrrolidine derivatives as conformational constrained propanamine derivatives. Preliminary *ex vivo* SERT-, NET- and DAT-binding/receptor occupancy data were acquired from these compounds and varying SERT, NET and DAT inhibition ratios were reported. Moreover, selected compounds were demonstrated to have antidepressant-like effects in rat forced swim test and mouse tail suspension test under their active doses, respectively. It was also claimed that the demonstrated antidepressant-like activity was not due to a general stimulant effect (**84**) (**Figure 14**) [92].

2.4.2 *Tetralone analogs*

Sertraline is a tetralone derived antidepressant of the SSRI class and remains one of the most prescribed antidepressants. Recently, the polymorphs of transnosertraline were claimed [93]. The conjugates are composed of Sertraline and Oligonucleotide complementary to a target nucleic acid sequence. The conjugates are useful for the delivery of the nucleic acid conjugated to a cell of interests and thus for the treatment of disease which require a down-regulation of the protein encoded by the target nucleic acid as well as for the delivery of imaging agents to the cells for diagnostic purpose [94].

Shao et al. from Sepracor investigated structural determinants for sertraline [95]. Preliminary pharmacological assays showed some tetralone-based analogs have potent inhibition on the neuronal uptake of NE, DA and/or SERT (**Table 5**).

La Roche claimed another tetralone analog, 1-(1H-indol-5-yl)-1, 2, 3, 4-tetrahydroquinolin-4-yl]-methyl-amine, which also shows affinities to human serotonin, norepinephrine or dopamine transporters (**97**) (**Figure 15**) [96].

2.5 Pyrrolidinyl derivatives

Diphenylprolinol (D2PM) (**98**) is a relatively mild norepinephrine-dopamine reuptake inhibitor of pyrrolidinyl class. Besides of pyrrolidinyl derivatives designed and prepared as conformationally constrained 3-Phenylpropan-1-amines, this structurally unique class was also extensively investigated (**Figure 16**).

F. Hoffmann-La Roche AG reported a series of pyrrolidinyl derivatives, for example, 5-(3-benzyl-pyrrolidin-3-yl)-1*H*-indole (**99**). These compounds were reported to show nanomolar binding affinities to human serotonin, norepinephrine and dopamine transporters and were further evaluated in analgesic models *in vivo*, such as formalin pain assay, colon pain assay and cold allodynia in rats with a chronic constriction injury of the sciatic nerve [97]. Another pyrrolidinyl derivative (**100**)with an aryl ketone in the structure was claimed to be more potent as TRIs [98].

Otsuka Pharmaceutical disclosed a series of N, N-substituted 3-aminopyrrolidine compounds. Most of these compounds have low-nanomolar activities against reuptake transporter, especially for compounds with a tert-butyl carbamate in the structure (**101 – 102**) (**Figure 17**) [99,100].

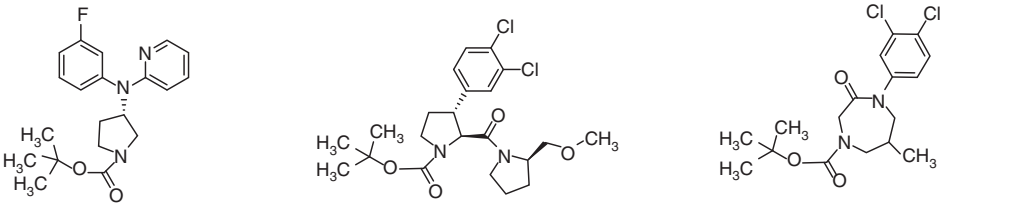
Takeda claimed another class of pyrrolidines with potent monoamine reuptake inhibition activities (**103**) [101]. Structurally similar diazepanes were also claimed with the structural motif of tert-butyl carbamate and 3, 4-dichlorophenyl groups unchanged [102].

2.6 Monocyclic piperidines, piperazines and aza-spiro analogs

2.6.1 *Piperidines (Table 6)*

In 2004, NeuroSearch described their work on the structural simplification of tropanes and yielded the claimed monocyclic piperidines and piperazines with TRI activities. Early disclosed 4-(2,3-dichloro-thiophenoxy) -1-methyl-piperidine (**104**) and 4-(2,3-dichloro-phenoxy)-piperidine (**104**) have balanced activities to inhibit the DA, NE and SERT reuptake [103]. 4-Benzyl-4-((3,4-dichlorophenoxy) methyl) piperidine (**106**) is also a potent triple monoamine reuptake inhibitor from 4-substituted piperidines [104]. *N*-phenyl-4-aminopiperidines (**107**) [105] are another class of reversed piperidines and the representative compound 1-(3, 4-dichlorophenyl)piperidin-4-ylamine shows low micromolar inhibition activities on monoamine reuptake transporters (**Figure 18**).

Monocyclic piperidines, piperazines and aza-spiro analogs might originate from simplified tropane structures or its structural variants, but it was not always the case. One class of piperidine-derived monoamine inhibitors were developed from fentanyl (**105**), a potent opioid analgesic. Early disclosed



101 Otsuka Pharmaceutical [99] **102** Otsuka Pharmaceutical [100] **103** Takeda Pharmaceutical [101]

Figure 17. Selected N, N-substituted 3-aminopyrrolidine compounds disclosed by Otsuka Pharmaceutical.

N-(1-phenethyl-piperidin-4-ylmethyl)-*N*-phenyl propionamide (**108**) remains significant affinities to μ opioid receptor (K_i = 37.3 nM), but its affinities to δ and κ opioid receptors are much lower [106]. In addition, this compound also shows micromolar scale TRI activities. The aromatic groups have been further refined to minimize opioid-like effects. The compounds *N*-(3,4-dichlorophenyl)-*N*-(1-((2-oxo -2*H*-chromen-6-yl)methyl)piperidin-4-yl) propionamide (**109**) [107] and *N*-(3,4-dichlorophenyl)-*N*-(1- (3-fluorophenethyl) piperidin-4-yl) propionamide (**110**) [108] show significantly decreased affinities on opioid receptors. Moreover, the removal of phenylethyl group from the fentanyl scaffold led to the discovery of potent monoamine reuptake inhibitors without opioid-like activities. N-(3,4-dichlorophenyl)-N-(piperidin-4-yl) propionamide (**111**) has potent inhibition activities on SERT and NA, thus is a dual SERT/NA inhibitor [109].

Piperidine-4-carboxamide derivatives (**112**) [110], piperidine-4-acetamide derivatives (**113**) [111] and piperidine-4-butyramide (**114**) derivatives [112] all have a reversed amide group in their structures. This structural motif could dramatically change the monoamine inhibition selectivity and led to the discovery of novel dual NA/dopamine reuptake inhibitors.

4-Benzhydryl-tetrahydropyridine derivatives are ring-expanded analogs of diphenylprolinol, a pyrrolidinyl-derived triple monoamine reuptake inhibitor. 4-Benzhydryl-1, 2, 3, 6-tetrahydropyridine (**115**) was disclosed to be selective SERT inhibitor [113]. But the compound (**116**) of 4-benzhydryl oxy-tetraalkyl-piperidine with more bulky substitution on the piperidine ring is much less active [114].

2.6.2 *Aza-spiro derivatives (Table 6)*

Aza-spiro derivatives are structural analogs of tropanes and piperidines. Firstly reported 3-(6-methoxynaphthalen-2-yl)-3,9-diazaspiro[5.5]undecane (**117**) is a triple monoamine reuptake inhibitor [115], while 9-(6-methoxynaphthalen-2-yl)-3-azaspiro[5.5]undec-8-ene (**118**) has more preferable dual SERT/DA reuptake inhibition activities [116]. By using the similar structural modification strategy of tropanes, further claimed 3-aza-spiro[5.5]undecane aryl ethers (**119**) and amines were found to be selective SERT inhibitors [117].

2.6.3 *Piperazines*

The prototype monoamine reuptake inhibitor from piperazines is trazodone, which is orally administrated active putative inhibitor of serotonin reuptake and is also a 5-HT_2 receptor antagonist. Trazodone (**123**) is commonly prescribed to treat depression and other psychiatric disorders [118]. Since this drug could be extensively metabolized in the liver, and Auspex Pharmaceuticals reported deuterium substitution strategy to improve their metabolic stability (**Figure 19**) [119].

Based on the scaffold of trazodone, NeuroSearch claimed 4-aryl-piperazin-1-yl-alkyl- benzoimidazo l-2-one derivatives and the disclosed compound, 1-(2-(4-(3,4-dichloro phenyl) piperazin-1-yl)ethyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one (**121**) is a highly selective SERT inhibitor, as it has 1000-fold activity more potent on SERT than on DA or NA reuptake [120]. A 4-indolyl-piperazin-1-yl derivative, 1-cyclohex-1-enyl-3-{2-[4- (1*H*-indol-6-yl)-piperazin-1-yl]-ethyl}-1, 3-dihydrobenzoimidazol-2-one (**122**) could strongly inhibit DA, NA and SERT reuptake at nanomolar scale [121].

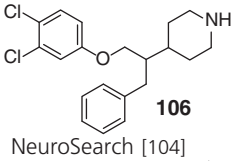
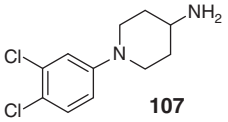
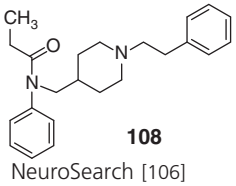
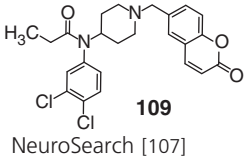
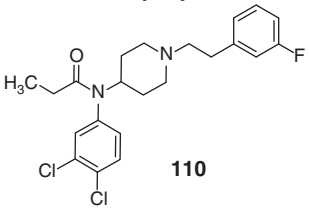
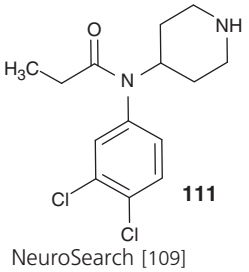
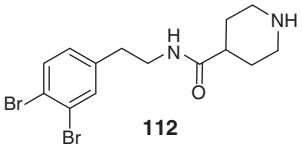
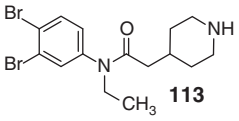
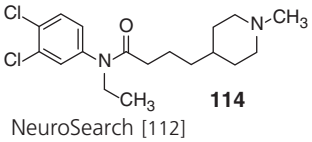
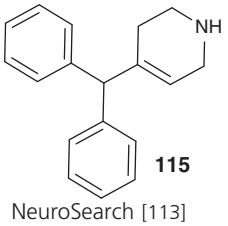
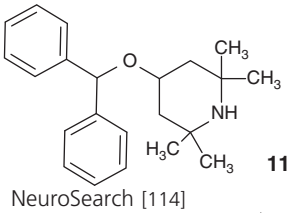
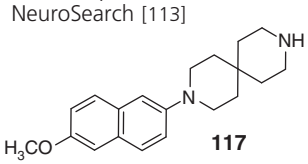
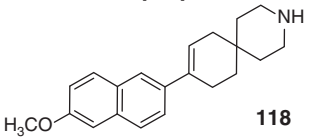
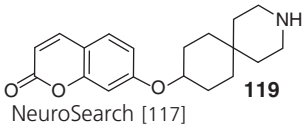
CSPC Zhongqi Pharmaceutical Technology described a series of benzothiophene alkanol piperazine derivatives. N^1-benzyl-N^4-[3-OH-3-(benzo[b] thiophene-3-yl)]propylpiperzine hydrochloride (**124**) shares similar biological activities with DOV21947 and Venlafaxine both *in vitro* and *in vivo* (forced swimming test) [122]. Another series of 1-butyl-2-hydroxyaralkyl piperazine derivatives was also disclosed and the selective compound N^1-benzyl-N^4-[1-butyl -2-(5′-chloro-6′methoxy-2′-naphthyl) hydroxyl-ethyl piperazine (**125**) has similar reuptake inhibition profile with Venlafaxine, but with much increased DA reuptake inhibition activities. This compound demonstrates similar antidepression effect with Venlafaxine *in vivo* with a IC_{50} of 11.8 mg/kg in mouse forced swimming test [123]. The optical isomers of this compound, with two chiral centers in its structure, were resolved by using a chiral camphor sulfonic acid [124] or mandelic acid [125] as the resolution reagent. Further biological activities of these isomers are not released.

2.7 Tetrahydroisoquinolines and analogs

2.7.1 *Tetrahydroisoquinolines*

Nomifensine (**126**) is 4-phenyl-substituted tetrahydroisoquinoline derivative which has been found to be a norepinephrine–dopamine reuptake inhibitor (NDRIs) due to its dual

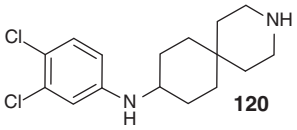
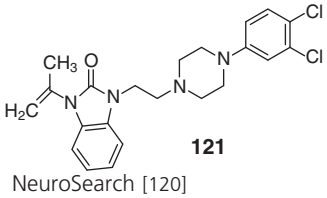
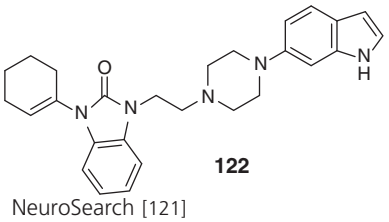
Table 6. Neurotransmitter uptake inhibition of piperidines and aza-spiro analogs.

Structure	Uptake inhibition*‡ IC_{50} (nM)			Structure	Uptake inhibition*‡ IC_{50} (nM)		
	SERT	NET	DAT		SERT	NET	DAT
 **106** NeuroSearch [104]	0.26	4.8	6	 **107** NeuroSearch [105]	27	150	400
 **108** NeuroSearch [106]	1300	370	730	 **109** NeuroSearch [107]	1100	930	1800
 **110** NeuroSearch [108]	1800	560	5600	 **111** NeuroSearch [109]	7.2	2	380
 **112** NeuroSearch [110]	120	3.1	4	 **113** NeuroSearch [111]	610	1.2	2.2
 **114** NeuroSearch [112]	800	12	6.9	 **115** NeuroSearch [113]	3.5	45	63
 **116** NeuroSearch [114]	26000	60	400	 **117** NeuroSearch [115]	80	550	450
 **118** NeuroSearch [116]	16	120	38	 **119** NeuroSearch [117]	2.0	86	1200

*The neurotransmitter uptake inhibitory effects of compounds were conducted in preparations of synaptosomes from different brain regions of male Wistar rats (NE: hippocampi; DA: corpi striate; SERT: cerebral cortices).

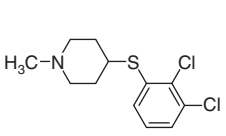
‡The test values are given as IC_{50} (the concentration (nM) of the test substance that inhibits the specific binding of ^{3}H-DA, ^{3}H-NE or ^{3}H-SERT by 50%).

Table 6. Neurotransmitter uptake inhibition of piperidines and aza-spiro analogs (continued).

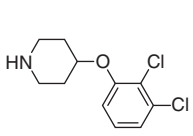
Structure	Uptake inhibition*‡ IC_{50} (nM)			Structure	Uptake inhibition*‡ IC_{50} (nM)		
	SERT	NET	DAT		SERT	NET	DAT
 **120** NeuroSearch [119]	2.3	1000	490	 **121** NeuroSearch [120]	1	1070	1100
 **122** NeuroSearch [121]	4.4	160	27				

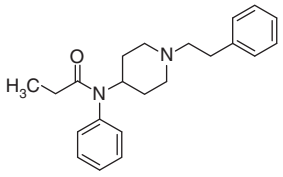
*The neurotransmitter uptake inhibitory effects of compounds were conducted in preparations of synaptosomes from different brain regions of male Wistar rats (NE: hippocampi; DA: corpi striate; SERT: cerebral cortices).

‡The test values are given as IC_{50} (the concentration (nM) of the test substance that inhibits the specific binding of ^{3}H-DA, ^{3}H-NE or ^{3}H-SERT by 50%).



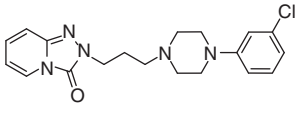
104 Neurosearch [103]



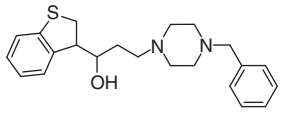


105 Fentanyl

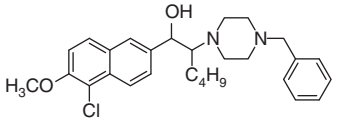
Figure 18. Early disclosed monocyclic piperidines and fentanyl.



123 Trazodone



124 SPC zhongqi pharmaceutical [122]

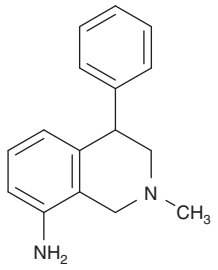


125 CSPC zhongqi pharmaceutical [123]

Figure 19. Trazodone and piperazines disclosed by CSPC Zhongqi Pharmaceutical.

inhibition activities against the reuptake of dopamine and other catecholamines [126]. It has been studied to show clinical efficacy for ADHD, and its antidepressive effect has also been noted. However, long-term administration of nomifensine resulted in fatal immune hemolytic anemia in a very small number of patients causing the manufacturer to discontinue this drug from the market (**Figure 20**).

Based on the basic tetrahydroisoquinoline scaffold of nomifensine, Molino et al. from AMR technology and Bristol-Meyers Squibb disclosed a series of aryl- and hetero-aryl substituted tetrahydroisoquinoline derivatives [127]. Substituted tetrahydroisoquinolines were investigated by substituting with multiple heteroaromatic groups. It has been claimed that the binding affinity (K_i values) of the monocyclic



126 Nomifensine

Figure 20. Nomifensine, a prototype of Tetrahydroisoquinolines.

heteroaromatic ring analogs are much less potent towards all three biogenic amine transporters than the compounds which possess bicylic heteroaromatic rings at the 4-position of 1,2,3,4-tetrahydroisoquinoline. This important structure feature led to unexpected improvements in potency and selectivity of these SNDRIs.

Other tetrahydroisoquinolines with 7-position substitution were described and the introduction of hetero-aryl group on this specific position were claimed to increase the binding affinities towards monoamine reuptakes of these compounds [128].

More specifically, (+)-*S*-7-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-4-(3, 4-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**127**), as well as its enatiomer, was claimed in another patent [129]. Unlike its (+)-isomer which has been described to be a selective SERT inhibitor, (-)-*R*–7-([1,2,4]triazolo [1,5-a]pyridin-6-yl)-4-(3, 4-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline was found to be a SNRI (SERT/NA dual inhibitor) since it demonstrated unexpected improved NET affinity. The minimum effective dose of the (+)-enatiomer in mouse tail suspension study was described to be 10 mg/kg. Its novel crystalline form SA-1 was claimed by Bristol-Myers Squib (**Figure 21**) [130].

Panacea Biotec investigated another series of tetrahydroisoquinolines with different substitutions. Some disclosed compounds (**128**) show similar reuptake inhibition activities to Venlafaxine [131].

2.7.2 Tetrahydrobenzazepines and tetrahydrobenzo-1,4-diazepines

Ring expansion investigations of the tetrahydroisoquinoline structure led to the discovery of series compounds of tetrahydrobenzazepines and tetrahydrobenzo-1,4-diazepines. Three series of compounds, aryl-/heteroaryl-substituted tetrahydrobenzazepines, aryl-/heteroaryl-substitutedtetrahydro benzo-1, 4-diazepines and aryloxy-/heteroaryloxy-substituted tetrahydrobenzazepines (**129 – 131**) were claimed to share similar inhibition activities against monoamine uptakes with tetrahydroisoquinolines both *in vitro* and *in vivo* assays (**Figure 22**) [132-134].

OTSUKA Pharmaceutical Co. claimed novel [1,4]benzodiazepines (**132**) with potent triple inhibition activities. These compounds are effective to reduce the immobility time in forced swimming test (**Figure 23**) [135].

2.8 Other classes of monoamine reuptake inhibitors

2.8.1 Tetracyclic dibenzo(e,h)azulenes

Based on the previous experience of dibenzo(e,h)azulene in the treatment of inflammatory diseases, GSK claimed novel tetracyclic dibenzo(e,h)azulene (**133**) with TRI activities [136]. Disclosed compounds have some binding affinities to SERT, DAT and NET, as well as antidepressive effects *in vivo* in tail suspension test, compared with the vehicle fluoxetine. Acetic acid-induced writhing test (visceral pain model) and formalin-induced paw-licking test (chronic pain model) suggested analgesia effects of these compounds (**Figure 24**).

2.8.2 Diaryl sulphides

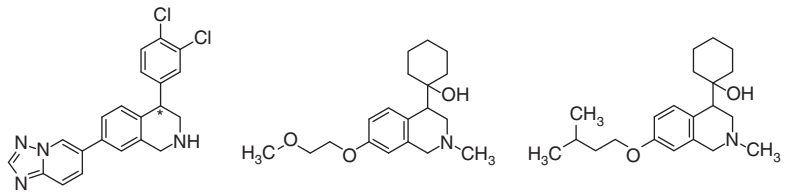
With an antidepressive compound diphenyl sulphides as the leading compound [137], Lundbeck investigated and claimed 2-(1H-indolylsulfanyl)-aryl amine derivatives (**134**). These compounds typically have an *in vitro* uptake inhibition (IC_{50}) of 5 µM or less to serotonin, norepinephrine or dopamine transporters, and some compounds were further claimed to have dual SERT/DA, SERT/NA or even TRI activities (**Figure 25**) [138].

2.8.3 Phloroglucinols and benzopyrans

Uliginosin B (**135**), extracted from the plant Hypericum polyanthemum and belonging to the class of phloroglucinols and benzopyrans, was found to inhibit the synaptomsomal uptake of DA more potently (IC_{50} 90 ± 38 nM) than that of SERT (IC_{50} 252 ± 13 nM) and NA (IC_{50} 280 ± 48 nM). These results suggest that the potential antidepressant effect of H. polyanthemum is related to the dopaminergic system. However, this effect does not appear to be dependent on a direct action of the substances on the monoamine transporter, which differs from other antidepressants inhibiting the reuptake of monoamines through competition for binding site on the transporter (**Figure 26**) [139].

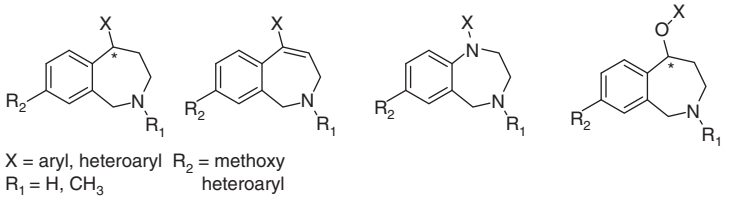
3. Expert opinion

The potential use of TRI in the treatment of depression, particular MDD, could meet unmet medical need in the therapeutic area significantly. The rational of TRI for the treatment of depression has its solid scientific and clinic bases. Two generations of monoamine transporters, SSRI and SNRI, both offered therapeutic benefit in the depression clinic treatment. The adjunctive use of bupropion also demonstrated improved efficacy for some patient population and improved safety profile to off set the downside of using SSRI or SNRI alone. These clinical outcomes suggested the possibility to fine tuning the depression treatment by modulating dopamine uptake inhibition. Theoretically, the mechanism of TRI is a well-characterized mechanism. From drug



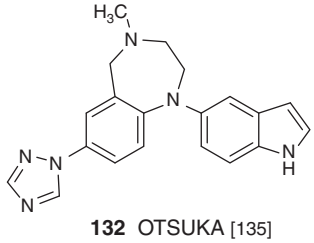
127 Albany [129] **128** Panacea Biotec [131]

Figure 21. Selected tetrahydroisoquinolines disclosed by Albanyl or Panacea Biotec.



129 AMR [132] **130** AMR [133] **131** AMR [134]

Figure 22. Selected tetrahydrobenzazepines and tetrahydrobenzo-1,4-diazepines disclosed by AMR.



132 OTSUKA [135]

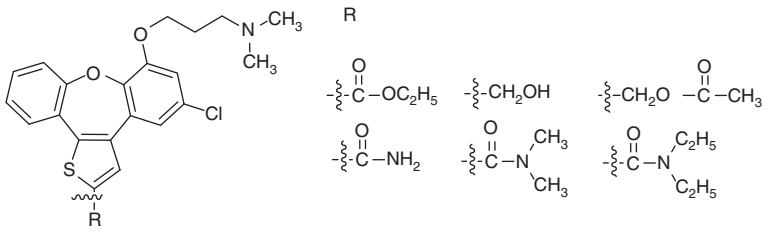
Figure 23. Selected tetrahydrobenzo-1,4-diazepine from the patent JP20111111419 and WO2009145357 disclosed by OTSUKA Pharmaceutical.

discovery and development perspective, the TRIs hunting mission is to create a "single" agent that has the activities against all three monoamine reuptake transporters (SERT, NET and DAT) with a "right ratio," safer and better tolerated for the treatment of depression. Of cause, there are potential uses for the TRIs that have different ratios for the treatment of other CNS diseases, such as pain, Parkinson's, ADHD, etc.

By reviewing past 7 years' patent applications, it is very clear that researchers in both academics and pharmaceutical industry were very successful in term of discovering the "agent" that potently inhibits all three monoamine transporters. Chemically, a series of diverse structures were explored and many interesting discovery have been made. These patent applications further enriched our knowledge of chemical space related to SERT, NET and DAT and paved a solid ground for using rational design approach to discovery novel TRIs.

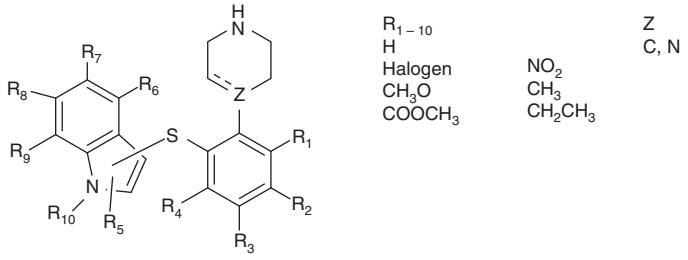
But, we have to admit that the progress for TRIs in general was slow. One of the causes is the complexity of CNS biology/pharmacology, which exhibits higher hurdles for CNS drug development. In practice, the biggest challenge is how to find an agent with a "right ratio." Technically, when we talk about "right ratio," it means the "right ratio" in human brain. That immediately raises the bar for the researchers in the TRIs discovery field, as we always start the compound evaluation in *in vitro* assays using recombinant cell lines and later, using rodent models for the *in vivo* efficacy studies. It is hard to define the reasonable criteria for the screen cascade. As a result, the learning/improving cycles for the SAR study were long and expensive. Fortunately, the progress in translational medicine provided us with more technical tools to measure the ratio of SERT, NET and DAT in rat, monkey and human brains. These tools, include positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), etc., enable us to determine the receptor occupancy in human and in nonhuman primates and provided great help to guide a more effective clinical trial.

Perhaps, we can refine our strategy to help to solve the "right ratio" problem in a philosophically easier way. In past 30 years, we have accumulated very rich knowledge and a huge set of clinic data by using SSRIs and SNRIs to treat depression. We have very good understanding on modulation of 5-HT and NE and their impact on the efficacy and side effects. For TRIs, the most important thing is to add right amount of DAT activity to the "ideal" SNRI (with a "rigth ratio" of SERT vs. NET). This is very easy to say but difficult to architecture. Luck is required for sure.



133 GSK [136]

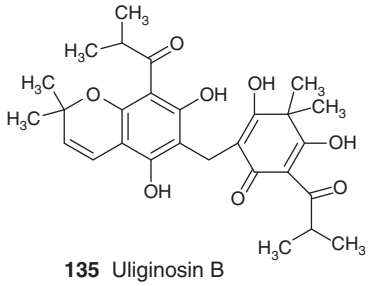
Figure 24. Selected Tetracyclic dibenzo(e,h)azulenes from the patent WO2006109190 disclosed by GSK.



R_{1-10}		Z
H		C, N
Halogen	NO_2	
CH_3O	CH_3	
$COOCH_3$	CH_2CH_3	

134 Lundbeck [138]

Figure 25. Selected Diaryl sulphides from the patent WO2006007843 disclosed by Lundbeck.



135 Uliginosin B

Figure 26. The structure of uliginosin B, from the patent WO2010092162 disclosed by Universite De Rouen.

Each monoamine neurotransmitter (5-HT, NE, and DA) is involved in multiple biological functions. Modulating these transmitters in an optimal range becomes extremely important. For example, certain level of DAT modulation can help to treat depression but too much of DAT activity will become a dose-limiting factor due to its stimulant effect; same for NET, you have to make a balance between depression treatment benefit (or the efficacy for neuropathic pain treatment) and cardiovascular effects (effects on the heart rate and blood pressure).The results from the PET studies using various SSRIs and TCAs at clinically efficacious doses all suggested that efficacy in the treatment of MDD requires a minimum SERT occupancy of ≥ 80% [140-143]. This finding also set a high bar to overcome for TRI discovery. Reexamining past 7 years' major set back in clinical trial, both NS-2359 and SEP-289 had high DAT activity, which caped the clinical dose to low to reach 'required' SERT occupancy to show clinical efficacy for the depression treatment.

Obviously, amitifadine (EB-1010) was, and may still be the front-runner for TRIs. The Phase IIb/IIIa trial results of amitifadine were somewhat disappointing. Amitifadine failed to meet primary endpoint in the trial for MDD. The good news is that the drug was well tolerated and, compared to paroxetine, it did not show weight gain, increase in blood pressure or heart rate and sexual dysfunction side effects. Euthymics concluded that the dose was set too low and plans to conduct a further trial using a higher dosage.

Since the translational medicine was not part of the trial, there is no way to know if the lack of efficacy was due to amitifadine's concentration lower than "required" SERT occupancy level. A further trial using a higher dosage will answer the question and give a clear answer to the fate of TRI.

Regardless the clinical setbacks, the past 7 years' endeavor is extremely valuable. Down to the road, using more translational medicine tools, researchers could further explore the chemical and biological space based on the SAR learned. It may not be just a dream to discovery a TRI that is more effective to the treatment of depression, safer, and more tolerable to the patients.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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